REMARKS

Applicants respectfully request reconsideration and allowance of the claims, as amended, in light of the remarks made herein. The Examiner is thanked for indicating that claim 3 is allowable.

Claims 1-23 and 27-40 are under examination in this application. Claims 1 and 2 have been amended. Support for each amendment can be found throughout the specification and from the claims as filed.

The amendments are introduced to address the Examiner's specific concerns and to more particularly point out and distinctly define the subject matter Applicants regard as the invention. No new matter has been added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Oath/Declaration

A oath or declaration was objected to as being improper. A new executed declaration is attached.

The Rejections Under §112 Are Overcome

Claims 1, 2, 4-23 and 27-40 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement, however, the Office Action contends that Applicants have only shown that they possessed SEQ ID NO:3 at the time the invention was made. It is unclear from the language of the Office Action whether this is an enablement rejection or a written description rejection, but it will be treated as an enablement rejection based on a similar rejection in the June 6, 2002 Office Action.

The attached Declaration of Dr. John Tagg describes a variant of the Salivaricin B protein, isolated from *Streptococcus mitis*. This protein has a histidine, rather than an arginine at position 13, and yet has substantially the same activity profile as the protein of SEQ ID NO:3, as shown in Exhibit 2 of the Declaration.

In addition, the paragraph beginning on page 6, line 13, details potential amino acid substitutions, particularly conservative substitutions. Further, the number of variants contemplated by the invention is very small. Indeed, the whole molecule itself is only 25 amino acids in length. It can be readily synthesized, and its activity determined, based on the teachings in the specification.

According to the Court of Appeals for the Federal Circuit in the case of *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988):

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is undue, not experimentation. The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted].

Id. at 1404.

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing many factors summarized in *In re Wands* (*Id.*), for example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Applying *Wands* to the instant facts, enablement is shown to exist. The amount of direction or guidance presented is high; working examples are present; the synthesis of polypeptides and the determination of antibacterial activity is routine; the relative skill of those in the art is high; and the predictability of the art is also high.

As stated in MPEP 2164.02, "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure... To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." MPEP 2164.02 goes on to say, "[p]roof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." Such evidence has not been provided here.

In fact, there is no evidence that the skilled artisan would have to practice undue experimentation. The Applicants have now disclosed two functional variants of Salivaricin B. The presence of working examples, taken in combination with the Declaration of Dr. Tagg, is more than sufficient to establish that a person skilled in the art could envision variants of SEQ ID NO:3 without undue experimentation.

Applicants have provided, for the first time, the protein of SEQ ID NO:3 and teachings of its antibacterial properties. By analogy with chemical cases, Applicants should be entitled to claim not only the specific protein, but those variants that are reasonably predicted to have the same activity. Therefore, the claims are commensurate with the scope of Applicants' contribution to the art.

Claims 21 and 22 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. It appears as though claim 1 was also included in this rejection.

Claim 1 has been amended for clarification. *Streptococcus* has also been spelled out, rather than abbreviated.

With respect to claims 21 and 22, the rejection is traversed. The Salivaricin B protein claimed is the primary antibacterial agent. The protein can be present in the formulation on its own. Claim 21 therefore specifies that the formulation may further comprise one or more secondary antibacterial agents. In claim 22 it is specified that the second antibacterial agent is selected from BLIS. Therefore it is clear that what is claimed is an additional BLIS in the formulation. Also comprehended is the situation where the S. salivarius strains K12 and K30 express both Salivaricin B and Salivaricin A2. Inclusion of both BLIS is said to render the formulation particularly bacteriocidal (see for example, page 16, last paragraph).

The objection seems to be that the microorganisms K12 and K30, which can be included in the formulation, but are not required, will produce both Salivaricin A and B. The claimed formulations of claims 21 and 22 may include 1) the protein of the invention only, 2) an organism which expresses the protein of the invention but not Salivaricin A, or, in some cases, 3) an organism which produces both Salivaricin A and the protein of the invention. Claims 21 and 22 are, therefore, a restriction on the earlier claims, as they require the presence of both the protein of the invention and of the secondary antibacterial agent. Going from an optional to a compulsory presence of the secondary antibacterial agent is clearly a limitation.

In view of these arguments and amendments, reconsideration and withdrawal of the rejections under §112 are solicited.

The Rejections Under 35 U.S.C. §102 and §103 Are Overcome

Claims 1, 2, 4-15, 21-23 and 27-40 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Caufield et al. Claims 1, 2, 4-23 and 27-40 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Caufield et al. These rejections are traversed, and will be treated collectively.

The Office Action has identified the Caufield reference as publishing a sequence that is a 86.9% match to SEQ ID NO:3. As a first point, our analysis suggests that this gives 84% (21 of 25 identical amino acids) homology, as is reflected in the "best local similarity" field of the computer search included with the Office Action.

As argued in the Amendment mailed on September 4, 2002, it is not enough to simply compare the overlap of the two sequences. The prior art does not disclose the shorter sequence to which the Examiner refers. To the contrary, Caufield et al. teaches how to produce a larger, 27 amino acid peptide.

If a direct comparison of the propeptides is carried out, then there are in fact six amino acids different between the sequences giving a percentage homology of 77.6%, which is less than 80% limit identified in the claims. There are also significant differences in the leader sequences of the two molecules if a full comparison of the sequences is carried out. The two additional residues at the N-terminus of the Caufield et al. sequence would be regarded by any skilled worker as important in defining the action spectrum of the molecule. This key component cannot be ignored.

The importance of the N terminus of the molecule is clear in the finding that a variant of the lantibiotic SA-FF22 with the first 4 amino acids missing had no biological activity (Jack and Tagg, 1991, In Nisin and novel lantibiotics. Jung, G. and Sahl H-G. eds, pp 171-179, ESCOM, Leiden; copy enclosed). Similarly, naturally occurring subtilin with a succinylated N-terminus was also reported to be less active (Chan et al., 1993 Biochem J. 291: 23 27; copy enclosed).

In summary, not only is the whole protein of the invention not disclosed in this citation, but there is simply no motivation to produce a C-terminal 25 amino acid sequence as the Examiner seems to suggest. In the interest of clarity, the claims have been amended to require "greater than 80% amino acid sequence identity" as opposed to "homology". In Applicants view, this restriction on the claims requires matching of the full sequences, not simply homology over the shorter sequence.

The Caufield et al. protein therefore has a different sequence, is derived from a different organism, and has a different functionality. The Applicant therefore submits that the specific *S. salivarius* antibacterial proteins with their identified bacteriocidal properties and requirement for greater than 80% homology with the protein isolated from S. salivarius strain K12 are not anticipated by the Caufield et al. sequence.

Further, there is no disclosure in Caufield et al. that teaches or suggests the antibacterial protein of the instant invention. As discussed above, it would not have been obvious to one of skill in the art that the 27 amino acid peptide described by Caufield et al. could be modified to produce the 25 amino acid peptide of the instant invention.

The Examiner is respectfully reminded of the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). No such teachings or suggestions are present in Caufield et al.

Claims 1, 2, 4-23 and 27-40 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ross et al., Tagg, Sanders et al., Matsushiro or Kawai et al. Claims 1, 2, 4-23 and 27-40 were also rejected under 35 U.S.C. §103(a) as allegedly obvious over Ross et al., Tagg, Sanders et al., Matsushiro or Kawai et al. taken with Caufield et al. These rejections are traversed, and will be treated collectively.

Initially, Applicants reiterate the arguments presented in the Amendment mailed on September 4, 2002. The Ross publication discloses Salivaricin A from Streptococcus salivarius 20P3. As noted in the background to the specification, while Salivaricin A demonstrated inhibitory activity against a number of streptococcal species, the activity was bacteriostatic rather than bacteriocidal. Salivaricin A, and microorganisms producing it, therefore do not provide a complete answer for controlling streptococcal infection. In contrast, Salivaricin B, which is the invention of the instant application, has been identified as bacteriocidal, as opposed to being simply bacteriostatic.

The cited Tagg article teaches S. salivarius having a high instance of BLIS production, particularly of Salivaricin A. No disclosure is made of the specifically claimed Salivaricin B protein, nor is it suggested in the article that any of the Salivarius strains identified produce Salivaricin B.

The Sanders document teaches the production of the antibiotic Enocin from S, salivarius strain K58. The antibiotic is stated to inhibit group A streptococci, including Streptococcus pyogenes. Enocin is a very small molecule (less than 200 Da, as estimated by Sephadex G25 chromatography). It appears to be a competitive inhibitor of pantothenate uptake by bacteria such as S. pyogenes, that are unable to synthesize their own pantothenic acid. Enocin is therefore also bacteriostatic not bacteriocidal (see column 1, lines 64-66), and differs significantly from the lantibiotic Salivaricin B presently claimed.

Matsushiro teaches lactic acid producing strains of S. salivarius which have the ability to degrade dental plaque. There is no suggestion that the Matsushiro strains produce the Salivaricin B protein, nor any suggestion that the strains are bacteriocidal, particularly against Streptococcus pyogenes, There is simply no motivation in this patent to produce the presently claimed proteins, organisms, and formulations.

Kawai also teaches various stains of streptococcus bacteria which can be used to deliver lactic acid bacteria to the intestine of a person who needs same. There is again no teaching of Salivaricin B or its properties, nor would it be obvious to produce same based on teachings in this document. Prior to the teachings of the instant application, it was not recognized that a bacteriocidal lantibiotic was being produced from S. salivarius, and accordingly, it would not have been obvious to isolated or purify proteins from the organisms disclosed in these references.

It is possible that the Examiner may be misinterpreting the statement at page 4, last paragraph, as meaning the all *S. salivarius* will produce the claimed BLIS. This is not in fact the case. A review of the Tagg paper above indicates that of the 1450 strains of *S. salivarius*, 45 are BLIS producing strains, and at that time 12 different types of BLIS were identified as being produced. It is therefore clear that only a low percentage of *S. salivarius* actually produce BLIS, and the number and effect of those BLIS may vary. This point is addressed in the accompanying Declaration by Dr. Tagg.

It is neither taught nor suggested by any of the documents in question that Salivaricin B is produced by any of these organisms, that it is active against *Streptococcus pyogenes*, and that it is a bacteriocidal strain as opposed to a bacteriostatic strain. None of the citations teach the production of the protein of the invention, nor has the Examiner established that there would have been any motivation for a person of ordinary skill to make the claimed proteins or variants as presently claimed. There is simply no reason to do so without an appreciation that this 25 amino acid protein is active in its own right, and has distinct bactericidal properties.

The Examiner alleges that Salivaricin B is not specifically claimed. This is not entirely correct. Salivaricin B is the antibacterial protein having the amino acid sequence of SEQ ID NO:3 or variants of it, so in that regard, it is claimed. "Salivaricin B" is simply the name allocated by the Applicants for convenience.

Moreover, because the Salivaricin B protein is novel and inventive, all of the protein and formulation claims, organisms, and method of treatment claims which produce or use Salivaricin B are similarly novel and inventive over and above the teachings of Caufield alone, or taken together with the secondary documents cited. In fact, there is no logical reason that the skilled artisan would combine Ross, Tagg, Sanders, Matsushiro, Kawai and Caufield. Caufield relates to what appears to be a *Lactococcus lactis* bacterial sequence with lantibiotic properties. Ross et al. is concerned with a particular *S. salivarius* which: produces Salivaricin A, Tagg with *S. salivarius* strains generally, Sanders with an *S. salivarius* which produces a tiny antibacterial protein, enocin, Matsushiro with *S. salivarius* which are not even shown to be lantibiotic producers, and Kawai with *Lactobacillus salivarius* which are similarly not shown to be lantibiotic producers.

Of the papas which do disclose BLIS products, none disclose the protein of SEQ ID NO:3, or one with equivalent properties. Again, as is discussed in the Declaration by Dr. Tagg, very few *S. salivarius* strains, in fact only 1.54% of the 780 strains tested to date, have been shown to produce the presently claimed protein of the invention. Absent the identification of the organism in many cases, the protein in other cases, or its desirable properties, there is simply no motivation in these documents to produce the antibacterial protein now claimed.

In view of the arguments and Declaration of Dr. Tagg, reconsideration and withdrawal of the art rejections are requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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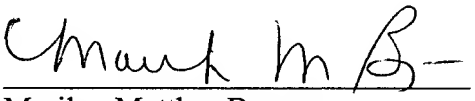
By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims

1. (Twice Amended) An isolated antibacterial protein obtainable[isolated] from [*S.*] *Streptococcus salivarius* strain K12 on deposit at Deutsche Sammlung von Mikroorganismen Und Zellkulturen GmbH, Braunschweig, Germany, accession number DSM 13084, having the following properties:[which has]

a) a molecular mass of approximately 2733 Da,[.] as determined by ion-spray mass spectrometry, and an[the] N-terminal amino acid sequence represented by SEQ ID NO: 1, or

b) an antibacterial [fragment or] variant of the antibacterial protein,[thereof] which variant has greater than 80% amino acid sequence identity[homology] with said protein.

2. (Twice Amended) An isolated antibacterial protein having the amino acid sequence of SEQ ID NO: 3 or an antibacterial [fragment or] variant of the antibacterial protein[thereof], which variant has greater than 80% amino acid sequence identity[homology] with said protein.